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Expanding the cellular molecular chaperone network through the ubiquitous cochaperones ☆

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ABSTRACT

Cellular environments are highly complex and contain a copious variety of proteins that must operate in unison to achieve homeostasis. To guide and preserve order, multifaceted molecular chaperone networks are present within each cell type. To handle the vast client diversity and regulatory demands, a wide assortment of chaperones are needed. In addition to the classic heat shock proteins, cochaperones with inherent chaperoning abilities (e.g., p23, Hsp40, Cdc37, etc.) are likely used to complete a system. In this review, we focus on the HSP90-associated cochaperones and provide evidence supporting a model in which select cochaperones are used to differentially modulate target proteins, contribute to combinatorial client regulation, and increase the overall reach of a cellular molecular chaperone network. This article is part of a Special Issue entitled: Heat Shock Protein 90 (HSP90).

1. Introduction

Numerous biological processes, which are driven by a variety of associated-pathways functioning through a cohort of proteins, maintain organismal and cellular homeostasis [1,2]. In “simple” unicellular organisms, such as budding yeast, ~6000 different proteins are produced to mediate cell viability under a range of physiological conditions. Each protein can be cast into an assortment of pathways to create an interconnected cellular network of biological processes. The efficiency of homeostasis, therefore, is linked to the capacity of proteins to transition both along and between pathways, which permits the network to function as a unified system [3]. However, the mechanism(s) used to achieve a dynamic environment for thousands of diverse proteins that efficiently supports metabolic equilibrium in the context of many internal and external signals is not understood. In this article, we suggest that a molecular chaperone network consisting of the classic ‘heat shock proteins’ in conjunction with a variety of cochaperones coordinates the proper behavior of an organism's diverse cellular proteome including the production of a dynamic protein environment.

Attention on how molecular chaperone systems influence cell viability and/or function has been myopic, as the focus is typically constrained to chaperones whose levels rise appreciably during physiological stresses such as Heat Shock Protein 70 (HSP70), HSP90 or HSP60 (i.e., HSP-chaperones) [4,5]. Yet, it is not the stress inducible characteristic that defines a protein as a molecular chaperone. Rather, demarcation as a molecular chaperone results from an empirical ability to suppress non-native protein aggregation in vitro [6]. Significantly, many non-HSP molecular chaperones display a comparable ability to prevent protein aggregation including the HSP90 cochaperones p23, Cdc37 and large immunophilins (e.g., FKBP52 and Cyp40) [7–9]. While an initial focus on the HSP-chaperones was a productive strategy for gaining insights into fundamental chaperone properties [5], assimilating the non-HSP chaperones into the current thinking is requisite for comprehending how a cellular molecular chaperone system promotes homeostasis.

But why should additional chaperones besides the ‘heat shock’ members be considered? After all, HSP70 and HSP90 account for 2–4% of the total protein mass of a eukaryotic cell and homologs of each generally exist in all cellular organelles/compartments [10–12]. These basic properties are seemingly sufficient to shepherd a cellular proteome especially since molecular chaperones typically transiently interact with client proteins—thereby providing ample ‘chaperone’ coverage of a cell's protein population. However, several key points need to be weighed when considering whether only a few chaperones might be able to cover an entire proteome including: 1) binding specificity of molecular chaperones; 2) functional impact of chaperone interactions; 3) inherent limitation of regulatory influences delivered by only a few chaperones.

2. Molecular chaperone binding determinants

Molecular chaperones are generally considered to have highly promiscuous binding abilities. This proposed trait helped rationalize the shared ability to suppress the aggregation of a wide-variety of

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non-native proteins in vitro [6]. In vivo studies on the HSP-chaperones further supports this contention including the findings that HSP70s bind nascent polypeptide chains as they emerge from ribosomes, HSP60s promote the assembly of divergent oligomeric protein complexes and HSP90s associate with many diverse signaling factors [5,11,12]. Hence, the in vivo and in vitro binding parameters for molecular chaperones are both seemingly broad.

Nevertheless, as mechanistic details emerge on how a chaperone recognizes its clients it is apparent that each one has a means for selective binding. For example HSP70s prefer short, extended peptide stretches consisting primarily of hydrophobic amino acids; however, not all peptides fitting this description are bound [13]. In contrast to HSP70s, HSP90s favor collapsed near native proteins that have a metastable characteristic [14,15]. Yet, HSP90s do not associate with all metastable proteins within a cell. Furthermore, HSP70s can associate with seemingly native proteins and HSP90s have been found to interact with apparently native, stable factors [12,16]. From these simplistic remarks, one can surmise that the principles governing chaperone–client protein selection are not fully understood. Yet, as no chaperone recognizes all cellular proteins, it is reasonable to conclude that guiding principles do exist to confer binding specificities for each chaperone.

Unfortunately, detailed binding rules for most molecular chaperones have not been deduced. However, given the growing wealth of high-throughput datasets it is possible to infer a binding range or at least a scope of interactions for many different proteins including numerous molecular chaperones. While this tactic has shortcomings (e.g., high-throughput work is often accomplished using indirect methods (i.e., genetic analysis) and false-positive/negative hits occur within large-scale work), it is adequate to gain an appreciation of the cellular pathways intersecting with the various chaperones and cochaperones. Hence, we exploited the considerable information in the *Saccharomyces* Genome Database (SGD) to gain an appreciation of the budding yeast HSP90 network that, given the conservation of the chaperone/cochaperone homologs, represents a general paradigm for HSP90 chaperone systems.

We elected to concentrate on the HSP90 cochaperone homologs that have been shown to have inherent chaperone activity (i.e., Cdc37, Cpr6, Cpr7 and Sba1) [7–9]. As a first step, we checked the relative depth of the available data for each. At the time of our analysis, SGD listed the number of unique interactors for each chaperone/cochaperone as Cdc37 (187), Cpr6 (66), Cpr7 (143), Hsc82 (831), Hsp82 (1179) and Sba1 (42). We amended the total Sba1 number to 344 by assimilating information from a recent publication that used both genetic and physical high-throughput tactics to identify Sba1 hits [17]. Our modification highlights an important point. Given the myopic focus on HSP90, the extent of data on the other chaperones/cochaperones is generally incomplete since multiple high-throughput trials have not been applied to each. Hence, the evaluation presented here should be further assessed as the amount of available data expands. Nevertheless, the current number of hits for the chaperones/cochaperones under consideration is fairly sizeable and therefore our analysis should provide guiding principles on how each factor contributes to the functional capacity of a cell.

In general, cochaperones are considered modifiers of a central molecular chaperone such as HSP90 [10,11,18]. The typical regulatory roles postulated for the cochaperones are two-fold including: 1) proper regulation of the chaperone's ATPase activity and 2) guidance of a chaperone to select client proteins [19]. All cochaperones are expected to modulate the ATPase rate through docking interactions; however, only cochaperones with inherent chaperone activity are able to guide client selection since contact with the substrate protein is required to direct the association. Notably, both of these responsibilities maintain the range of cochaperone action within the framework of the central chaperone's realm. Thus, based upon these two roles, cochaperones would only be expected to affect proteins modified by their cognate HSP-chaperone (e.g., HSP90).

To gain an initial appreciation of how cochaperones might intersect with an HSP90 chaperone, we took an uncomplicated tactic and compared all SGD curated genes associated with Cdc37, Cpr6, Cpr7, Hsp82 and Sba1. The interacting genes were displayed in a Venn diagram with Hsp82 as the focus and the cochaperones organized to maximize the overlap between each. Remarkably, none of the cochaperone-associated gene pools were confined within the boundaries of the Hsp82-linked genes (Fig. 1). Rather, less than 50% of the cochaperone hits (Cdc37 42%, Cpr6 39%, Cpr7 44%, Sba1 30%) were in the Hsp82 catalog. At face value, this weak correspondence indicates a general disconnect between the clients interacting with Hsp82 and the cochaperones. Of note, a similar low coincidence was found when the cochaperone pools were compared to the collection of genes associated with both yeast HSP90s (i.e., Hsc82 and Hsp82) (1260 total; data not shown). To account for the unexpectedly low overlap, we suggest that these cochaperones have HSP90-independent cellular activities in addition to their standard roles of modulating HSP90's ATPase or client binding activities.

It is important to consider that our simple bioinformatic analysis is based upon resources frequently collected by high-throughput methods that have the previously noted caveats. In addition, identified associated genes/proteins are not always surveyed for all potential chaperone/cochaperone interactions and therefore the profile data is incomplete. Nevertheless, given the universally low coincidence between each cochaperone-associated pool and Hsp82, it is reasonable to conclude that the cochaperones have cellular roles that are independent of HSP90. Although there are many potential cellular applications for autonomous cochaperone activities, we will focus on the following: 1) differential modulation of target proteins; 2) combinatorial client regulation; and 3) expansion of the molecular chaperone network.

3. Opposing operational effects mediated by molecular chaperones

The HSP90 chaperone machine generally is viewed as a system for maintaining metastable factors in a functional state. For example, upon small molecule inhibition of HSP90 numerous kinases, which

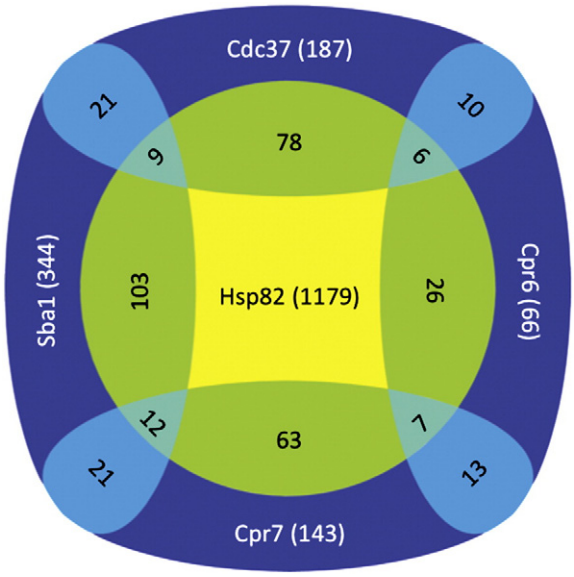

Fig. 1. The Hsp82, Cdc37, Cpr6, Cpr7 and Sba1 associated-genes are comparatively independent. The ORFs known to interact physically or genetically with Hsp82, Cdc37, Cpr6, Cpr7 and Sba1 were determined using the *Saccharomyces* Genome Database (SGD) and displayed in a Venn diagram. The total number of interactors for each chaperone/cochaperone is shown in parentheses, the relative overlap between Hsp82 and each cochaperone is provided, and the cochaperones were arranged to maximize the overlay.

form long-lived interactions with HSP90, aggregate or are degraded [20]. It has become apparent, however, that components of the HSP90 system also form short-lived, functional associations with stable proteins such as transcription factors and reverse transcriptases [16]. In contrast to the metastable clients that require HSP90 for solubility, the interactions with stable proteins appear to be regulatory in nature. Intriguingly, the modulatory impact of HSP90 and certain cochaperones with native clients often differs (i.e., opposing effects are conferred by each). Hence, the involved cochaperone appears to utilize its inherent chaperone function to offset HSP90.

For example, HSP90s have been shown to promote the DNA binding activities of numerous transcription factors including aryl hydrocarbon receptor (AhR), myogenic determination (MyoD) protein, hypoxia-inducible factor 1 (HIF-1), glucocorticoid receptor (GR) and p53 [21–26]. Additionally, HSP90s foster DNA binding by the specialized reverse transcriptase telomerase [27,28]. Intriguingly, the p23 cochaperone does not support this HSP90 ability, as might be anticipated from the standard proposed roles of a cochaperone. Rather, p23s appear to work independently to induce dissociation of either DNA-bound transcription factors or telomerase [29–31]. Together, the independent HSP90 and p23 actions create a dynamic behavior for various DNA-binding proteins, which is essential for multistep pathways [3].

By targeting the central component (e.g., transcription factor) responsible for nucleating various requisite structures along a pathway, the HSP90 and p23 chaperones enable efficient mobility of the target path by coordinating the rapid assembly and disassembly of sequential complexes. For example, initiation of gene transcription typically requires the marking of chromatin elements, the removal of heterochromatin factors, the recruitment of RNA polymerase and the activation of the polymerase enzyme [32]. Though the order of events varies with promoter and cell contexts, in a given setting the different complexes work in a set order to achieve proper gene regulation. By maintaining the central transcription factors in a dynamic state HSP90 and p23 allow the individual structures to exchange rapidly, which promotes efficient transitions between complexes and avoids competitive binding events since each component only interacts transiently with the DNA. The ability of HSP90 and p23 to associate with each other likely permits a 'handing off' of the transcription factor. Basically, p23 dissociates the DNA-bound protein, direct contact between p23 and HSP90 initiates a reassembly phase in which HSP90 promotes rebinding of the factor to DNA and formation of the next transcription complex. Essentially, the HSP90–p23 interaction serves as an intermediate step between the different assemblies of a target pathway.

In contrast to the standard model in which the cochaperones work through HSP90 to support metastable clients, our speculative model for chaperone effects with stable proteins has significant variances. Briefly, we are proposing that cochaperones deliver independent and distinct effects on a client rather than transducing an influence through HSP90. By incorporating both HSP90-dependent and -independent cochaperone action the breadth of cochaperone-mediated regulatory action is appreciably increased.

Regrettably, our current understanding of sovereign cochaperone functions is limited since most work focuses on the impact of HSP90 on a client or the influence of a cochaperone on HSP90's ATPase activity. As chaperone investigations expand to include potential independent cochaperone functions, we anticipate that autonomous cochaperone roles will become common. Certainly our simplistic breakdown of the yeast HSP90- and cochaperone-associated genes supports this contention (Fig. 1). It will be exciting to discover the various means by which cochaperones contribute to client protein regulation both separately and in conjunction with HSP90.

4. Molecular chaperone directed combinatorial protein regulation

We were intrigued by our initial bioinformatic result (Fig. 1), as HSP90 and its cognate cochaperones are generally believed to modify the same cellular pathways. Yet, the lack of overlap at individual ORFs might imply differently. To explore this contention we performed a further in silico analysis to determine the cellular processes linked to each group of chaperone/cochaperone-associated genes. Since factors often work in more than one cellular process, we considered all potential functions for each ORF when partitioning the gene pools into the various cellular processes using a GO Slim analysis. As the number of hits for each protein varies, we normalized the data by calculating the enrichment in each category relative to all annotated yeast genes. In general, the cochaperones and Hsp82 were not significantly enriched in any particular process (Fig. 2). Rather, these proteins appear to act like typical molecular chaperones and serve a broad range of cellular processes. Still, several enhancements were apparent for individual cochaperones including cell cycle, cell membrane organization, chromosome segregation, meiosis, nuclear organization, protein folding and vesicle-mediated transport (Fig. 2). Notably, prior functional studies support specific roles for chaperones/cochaperones in several of the enriched categories including Cpr7 in cell cycle and Sba1 in vesicle-mediated transport [17,33]. Overall, however, the patterns for Hsp82 and the four cochaperones were quite similar. Given the relatively low overlap in actual ORF targets (Fig. 1), how are the cochaperones and Hsp82 effectively serving many of the same processes?

Typically, cellular pathways operate through protein complexes rather than individual protein units. Thus, we examined whether Hsp82 and the cochaperones might link to common processes by interacting with different subunits of a protein complex. We again exploited the SGD database and determined the stable protein structures with subunits associated with Hsp82, Cdc37, Cpr6, Cpr7 or Sba1. For illustrative purposes, we plotted the complexes associated with each cochaperone along with the Hsp82-connected structures (Fig. 3). In sum, the total number of stable structures linked to each are the following: Hsp82 (213), Cdc37 (78), Cpr6 (40), Cpr7 (66) and Sba1 (88). To gain a better appreciation, we normalized these values to the total number of hits for each chaperone/cochaperone to acquire the following percentiles: Hsp82 (18%), Cdc37 (42%), Cpr6 (61%), Cpr7 (46%) and Sba1 (25%). The normalized figures reveal the propensity of each to associate with stable protein structures with Cpr6-linked factors showing a high tendency followed by Cpr7 and then Cdc37. Based on the percentiles, Hsp82 and Sba1 do not appear to favor components of stable complexes. Thus, one potential determinant to discriminate chaperone/cochaperone dependence might be the propensity of a client to function in a protein assembly.

Significantly, the most prominent feature of our stable complex analysis was the finding that the majority of the cochaperone-associated structures were also linked to Hsp82 (Fig. 3). For example, 70 of 78 Cdc37 interacting complexes were connected to Hsp82. In sum, ~90% of the cochaperone-linked stable structures were within the Hsp82 set. Remarkably, the convergences predominantly involve different subunits of the same protein complexes.

While there are several plausible reasons to account for this relationship, we favor two concepts: 1) the cochaperones and Hsp82 cooperate to assemble and/or disassemble protein complexes or 2) by interacting with more than one subunit of a complex a greater level of chaperone-mediated regulation might be gained (i.e., cooperative effect). In a recent publication, we found that Sba1 and Hsp82 do indeed physically bind to the predicted stable protein complexes and that the chaperone-targeted subunits were often juxtaposed [17]. Hence, the potential for simultaneous modulation of two substrate proteins while maintaining the cochaperone in close proximity to Hsp82 (i.e., chaperone–cochaperone communication) is a viable route of client regulation.

In addition to the paired chaperone–cochaperone linked stable structures, further study of the data revealed that select complexes had numerous cochaperones interacting with multiple subunits. For example, RNA polymerase, preribosome, polysome, proteasome, microtubule, kinetochore, nuclear pore and chromatin remodeling

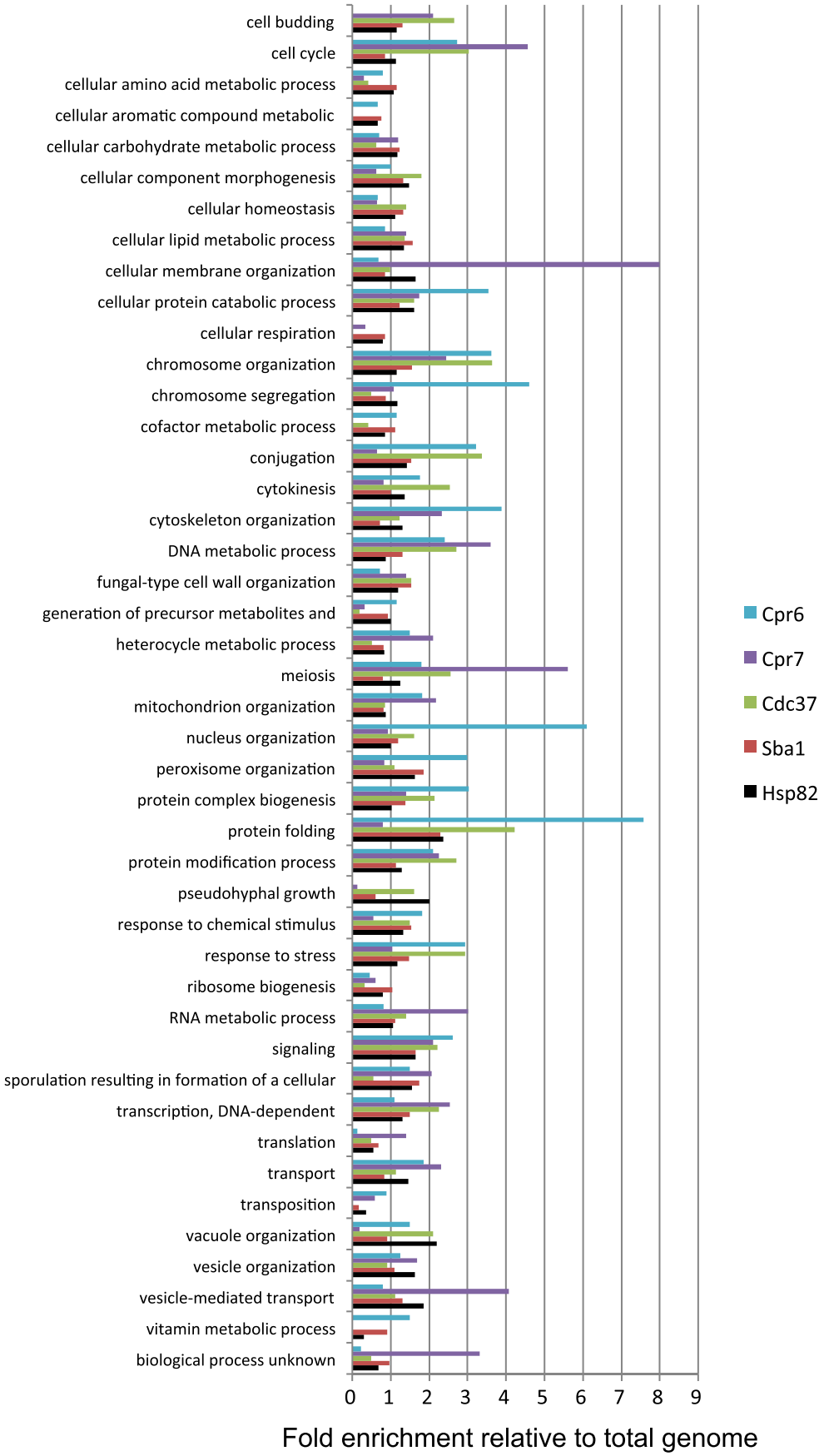

Fig. 2. Hsp82, Cdc37, Cpr6, Cpr7 and Sba1 interact with genes functioning in common cellular processes. All the ORFs associated with Hsp82, Cdc37, Cpr6, Cpr7 and Sba1 were categorized using a GO Slim analysis. The relative enrichments in the indicated cellular process for each chaperone/cochaperone are shown.

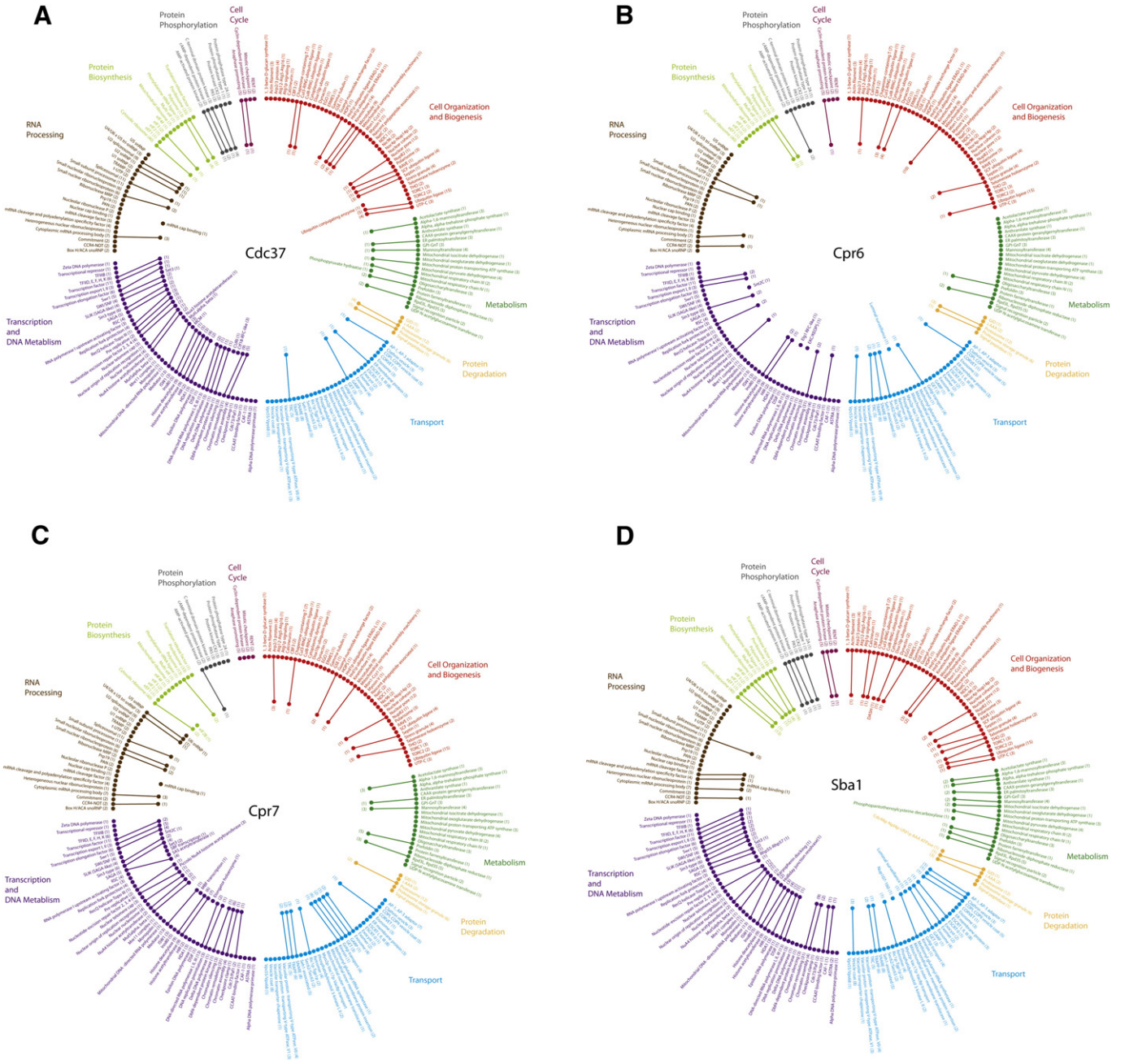

Fig. 3. Stable protein complexes associated with the various cochaperones are commonly linked to Hsp82. Using a GO Slim analysis the stable protein complexes associated with Hsp82, Cdc37, Cpr6, Cpr7 and Sba1 were determined. Each outer circle represents structures with at least one Hsp82-interacting subunit and the inner circles have complexes associated with Cdc37 (A), Cpr6 (B), Cpr7 (C) or Sba1 (D). The lines connect protein assemblies with common hits between Hsp82 and the indicated cochaperone.

complexes associated with many, if not most, HSP90-linked cochaperones. It is conceivable that certain structures, particularly sizeable ones, require a multifaceted chaperone-mediated assembly/regulatory pathway. Although empirical studies are needed to determine the functional relevance of these multi-point interactions, the potential for multidimensional chaperone action on discrete protein complexes suggests a new avenue for chaperone action within the cell.

5. Dynamic molecular chaperone system governs proteostasis

The ability of cochaperones and Hsp82 to interact with stable protein complexes offers a partial resolution as to why these factors appear to operate within the same cellular processes despite a low overlap in identical associated-genes (Figs. 1 and 2). Yet, the combination of individual ORFs and stable structures is likely insufficient to account for the high correlation in shared cellular processes. To rationalize how the cochaperones and Hsp82 might further interface, we suggest that they merge onto common processes by intersecting at different points along biological pathways.

Ribosome biogenesis and vesicular-mediated protein transport highlight this potential as both paths have a relatively large number of cochaperone and Hsp82 interactors yet few hits are with the same ORF or structure. Given the complexity and extensive use of protein assembly/disassembly events along these pathways it is reasonable to envision a significant requisite for chaperone action in

order to efficiently drive these processes. Although it is plausible that the HSP-chaperones (i.e., HSP90 and HSP70) provide sufficient coverage, we propose that the cochaperones also directly contribute using their inherent chaperone activities. Incorporating cochaperones would provide the previously described benefits—broader substrate binding capacity and an ability to differentially regulate clients. For example, Hsp82 impacts protein transport by binding to the vesicle-tethering complexes COG and TRAPP [34] whereas Sba1 modulates transport by altering Golgi-associated protein mannosylation [17]. Hence, p23 and HSP90 function at distinct points along the transport pathway in order to influence the overall efficiency of the process.

By intersecting at individual proteins, protein complexes and protein pathways, cochaperones form a triaxial relationship with HSP90 and cellular processes. We suspect that these crossroads, along with the independent cochaperone clients, provide an efficient means to expand the reach of the HSP90 molecular chaperone system beyond the limited hub of one or two proteins (i.e., Hsp90 and Hsc90). Therefore, in addition to merely guiding HSP90s to clients or modulating the ATPase rate, certain cochaperones use their innate chaperone abilities to distinctively modulate proteins and cellular pathways to form a more elaborate cellular chaperone grid. The comprehensive system would create an accessible and pliable mechanism to rapidly tune both protein folding and client regulation. Together, the inclusive molecular chaperone network would meet the immediate and specific needs of a cell to insure homeostasis under ever-fluctuating physiological conditions.

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